Clinical Product Review

This product review was developed by Novo Nordisk Inc.

ONCE-WEEKLY
wegovy®
semaglutide injection 2.4 mg

Indications and Usage[1]

Wegovy® (semaglutide) injection 2.4 mg is indicated in combination with a reduced calorie diet and increased physical activity:

- to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight
- to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged 12 years and older with obesity and adults with overweight in the presence of at least one weight-related comorbidity

Limitations of Use[1]: Wegovy® contains semaglutide. Coadministration with other semaglutide-containing products or with any GLP-1 receptor agonist is not recommended

Important Safety Information[1]

WARNING: RISK OF THYROID C-CELL TUMORS

- **In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Wegovy® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined**
- **Wegovy® is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Wegovy® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Wegovy®**

Please see additional Important Safety Information throughout.
Please click here for Prescribing Information, including Boxed Warning.

The Only FDA-Approved GLP-1 RA Clinically Proven to Treat Obesity and Reduce the Risk of MACE (major adverse cardiovascular events)

Wegovy® is the first once-weekly GLP-1 receptor agonist (GLP-1 RA) analog approved by the U.S. Food and Drug Administration (FDA) as an adjunct to a reduced-calorie diet and increased physical activity to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight. Wegovy® is also indicated to reduce excess body weight and maintain weight reduction long term in:

- Adults and pediatric patients aged 12 years and older with obesity
- Adults with overweight in the presence of at least one weight-related comorbid condition[1]

Important Safety Information

Contraindications

- Wegovy® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2, and in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in Wegovy®. Serious hypersensitivity reactions, including anaphylaxis and angioedema have been reported with Wegovy®

Mechanism of Action[1]

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 RA that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological regulator of appetite and caloric intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. Animal studies show that semaglutide distributed to and activated neurons in brain regions involved in the regulation of food intake.

The exact mechanism of cardiovascular risk reduction has not been established.

Clinical Studies

The major adverse cardiovascular events (MACE) risk reduction indication was based on SELECT, a cardiovascular outcomes trial, which was a randomized, placebo-controlled, double-blind trial to determine the effect of once-weekly Wegovy® 2.4 mg vs placebo (1:1 randomization) for time to first MACE when added to the current standard of care.[1] The primary end point, MACE, was the time to the first occurrence of a three-part composite outcome that included cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.[1]

The safety and efficacy of Wegovy® for the weight management trials was studied in the STEP clinical trial program. This program included trials in adults and 1 trial in pediatric patients, to evaluate Wegovy® for weight reduction and long-term maintenance of body weight in conjunction with lifestyle intervention (diet and exercise counseling).[1]

STEP 1, 2, 3, and 5 were randomized, double-blind, and placebo-controlled trials; STEP 4 was a randomized, double-blind, placebo-controlled withdrawal trial with a 20-week run in; and STEP 6 was a randomized, double-blind, placebo-controlled trial that investigated 2 different maintenance doses of Wegovy®.[1,2] STEP TEENS was a double-blind, parallel-group, randomized, placebo-controlled trial.[3] Inclusion and exclusion criteria for the studies are listed in Table 1.

Coprimary end points for STEP 1, 2, 3, and 6 were mean percentage change in body weight from baseline to week 68 and the percentage of patients who achieved ≥5% weight reduction from baseline to week 68.[1] For STEP 4, the primary end point was mean percent change in body weight from randomization (week 20) to week 68.[1] For STEP 5, the coprimary end points were percent change in body weight from baseline to week 104 and the percentage of patients who achieved ≥5% weight reduction from baseline to week 104.[2] For STEP TEENS, the primary end point was percent change in BMI from baseline to week 68, while a reduction in BMI of at least 5% was one of the supportive secondary end points.[3] Secondary end points for all studies included waist circumference and select cardiometabolic parameters.

SELECT: Cardiovascular outcomes trial in adult patients with cardiovascular disease and either obesity or overweight

SELECT was a randomized (1:1), placebo-controlled, double-blind trial that enrolled 17,604 adult patients to determine the effect of once-weekly Wegovy® 2.4 mg (n=8803) vs placebo (n=8801) (with a 16-week dose escalation period) on time to first MACE when added to the current standard of care, which included management of cardiovascular risk factors and individualized healthy lifestyle counseling (including diet and physical activity).[1,4,5]

For the primary composite end point (Figure 1), Wegovy® 2.4 mg significantly reduced the risk for the first occurrence of MACE (6.5%) when compared to placebo (8%). Hazard ratio: 0.80 (95% CI, 0.72-0.90), $p<0.001$. Table 2 shows the results for key and other secondary endpoints. The median follow-up for the trial was 41.8 months.[1,5]

STEP 1: Weight management in the general adult population

STEP 1 was a 68-week randomized trial that enrolled 1961 adult patients with obesity or with overweight and at least 1 weight-related comorbid condition; patients with type 2 diabetes were excluded.[1] Patients were randomized in a 2:1 ratio to either Wegovy® 2.4 mg (n=1306) or placebo (n=655) (with a 16-week dose escalation period), both in conjunction with lifestyle modifications.[1]

For the coprimary end points (Figure 2), after 68 weeks, a statistically significant reduction in body weight was observed in patients treated with Wegovy® (-14.9%) compared with those treated with placebo (-2.4%). A greater proportion of patients achieved ≥5% weight reduction with Wegovy® (83.5%) compared with placebo (31.1%).[1] During the trial, 17% of patients in the Wegovy® arm discontinued treatment compared with 22% in the placebo arm.[6]

Important Safety Information

Warnings and Precautions

- **Risk of Thyroid C-Cell Tumors:** Patients should be further evaluated if serum calcitonin is measured and found to be elevated or thyroid nodules are noted on physical examination or neck imaging
- **Acute Pancreatitis:** Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, including Wegovy®. Observe patients carefully for signs and symptoms of acute pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting). If acute pancreatitis is suspected, discontinue Wegovy® and initiate appropriate management

Changes in waist circumference and select cardiometabolic parameters were evaluated as secondary endpoints (Table 4).[1]

STEP 2: Weight management in adults with type 2 diabetes mellitus

STEP 2 was a 68-week trial that enrolled 807 patients with type 2 diabetes and BMI ≥27 kg/m^2. Patients included in the trial had an A1c of 7% to 10% and were treated with either diet and exercise alone or 1 to 3 oral anti-diabetic drugs (metformin, sulfonylurea, glitazone, or sodium-glucose co-transporter 2 inhibitor). Patients were randomized in a 1:1 ratio to receive either Wegovy® 2.4 mg or placebo (with a 16-week dose escalation period), both in conjunction with lifestyle modification.[1]

For the coprimary end points (Figure 2), after 68 weeks, a statistically significant reduction in body weight was observed in patients treated with Wegovy® (-9.6%) compared with those treated with

TABLE 1. Key Eligibility Criteria in SELECT, STEP 1-6, and STEP TEENS[1-11,13,14]

Study	Inclusion Criteria	Exclusion Criteria
SELECT	• Adults (aged ≥45 years) with BMI ≥27 kg/m^2 • Have established cardiovascular disease as evidenced by at least 1 of the following: prior myocardial infarction; prior stroke (ischemic or hemorrhagic stroke); or symptomatic peripheral arterial disease	• Myocardial infarction, stroke, or hospitalization for unstable angina or transient ischemic attack within 60 days before screening • History of type 1 or type 2 diabetes • Treatment with glucose-lowering agents (including GLP-1 RAs) within 90 days before screening • Hemoglobin A1c ≥48 mmol/mol (6.5%)
STEP 1, 3, 4, 5	• Adults with obesity (BMI ≥30 kg/m^2) OR • Overweight (BMI ≥27 kg/m^2) with at least 1 weight-related comorbid condition[a]	• Type 2 diabetes • Hemoglobin A1c ≥48 mmol/mol (6.5%) • Self-reported change in body weight of more than 5 kg within 90 days before screening
STEP 2	• Adults with type 2 diabetes AND • BMI ≥27 kg/m^2	• Self-reported change in body weight of more than 5 kg within 90 days before screening • Renal impairment, as determined by glomerular filtration rate <30 mL/min/1.73 m^2 (<60 mL/min/1.73 m^2 in subjects treated with sodium-glucose cotransporter 2 inhibitors) • Uncontrolled and potentially unstable diabetic retinopathy or maculopathy
STEP TEENS (pediatric trial)	• Pediatric patients (aged ≥12 years to <18 years) • BMI corresponding to ≥95th percentile standardized for age and sex	• Prepubertal subjects • History of type 1 diabetes • Self-reported change in body weight of more than 5 kg within 90 days before screening • Subjects with secondary causes of obesity • Uncontrolled and potentially unstable diabetic retinopathy or maculopathy (for patients with type 2 diabetes)
STEP 6	• East Asian adults with BMI ≥35 kg/m^2 and at least 1 weight-related comorbid condition[b] OR • BMI of 27 kg/m^2 to 34.9 kg/m^2 and at least 2 weight-related comorbid conditions[b]	• Self-reported changes in body weight of 5 kg or more 90 days before screening • Previous or planned obesity treatment with surgery or any medication for the indication of obesity

[a]Hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease.[6]
[b]Comorbidities per Japan Society for the Study of Obesity guidelines; one comorbidity had to be hypertension, dyslipidemia, or, in Japan only, type 2 diabetes.

Important Safety Information

Warnings and Precautions, continued

- **Acute Gallbladder Disease:** Treatment with Wegovy® is associated with an increased occurrence of cholelithiasis and cholecystitis. The incidence of cholelithiasis and cholecystitis was higher in Wegovy® pediatric patients aged 12 years and older than in Wegovy® adults. In clinical trials in adult patients, cholelithiasis was reported by 1.6% of Wegovy® patients and 0.7% of placebo patients. Cholecystitis was reported by 0.6% of Wegovy® patients and 0.2% of placebo patients. In a clinical trial in pediatric patients aged 12 years and older, cholelithiasis was reported by 3.8% of Wegovy® patients and 0% placebo patients. Cholecystitis was reported by 0.8% of Wegovy® pediatric patients and 0% placebo patients. Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in Wegovy® patients than in placebo patients, even after accounting for the degree of weight loss. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated

FIGURE 1. Cumulative Incidence Function: Time to First Occurrence of Mace[1,5]

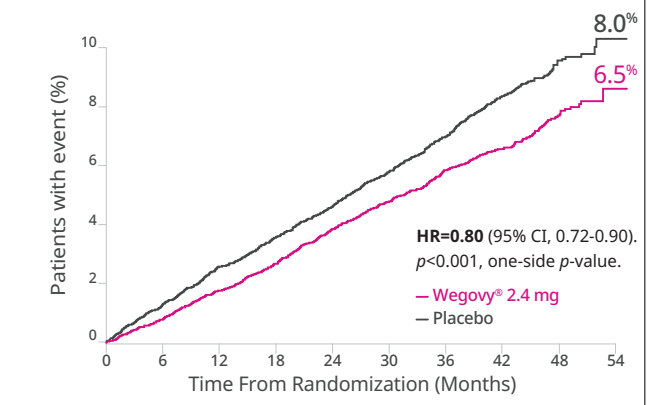


TABLE 2. Treatment Effect for MACE and Other Events in SELECT[1,5]

	Patients with events, n (%)		
	Placebo (N=8,801)	Wegovy® (N=8,803)	Hazard Ratio (95% CI)
Primary composite endpoint			
Composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke[a]	701 (8.0%)	569 (6.5%)	0.80 (0.72; 0.90)[b,c]
Key secondary endpoints			
Cardiovascular death[d]	262 (3.0%)	223 (2.5%)	0.85 (0.71; 1.01)
All-cause death[e]	458 (5.2%)	375 (4.3%)	0.81 (0.71; 0.93)
Other secondary endpoints			
Fatal or non-fatal myocardial infarction[f]	334 (3.8%)	243 (2.8%)	0.72 (0.61; 0.85)
Fatal or non-fatal stroke[f]	178 (2.0%)	160 (1.8%)	0.89 (0.72; 1.11)

[a]**Primary endpoint**

[b]***p*<0.001, one-sided *p*-value.**

[c]**Adjusted for group sequential design using the likelihood ratio ordering.**

[d]**Cardiovascular death was the first confirmatory secondary endpoint in the testing hierarchy and superiority was not confirmed.**

[e]**Confirmatory secondary endpoint. Not statistically significant based on the prespecified testing hierarchy.**

[f]**Not included in the prespecified testing hierarchy for controlling type-I error.**

placebo (-3.4%). A greater proportion of patients achieved ≥5% weight reduction with Wegovy® (67.4%) compared with placebo (30.2%).[1] During the trial, 6.2% of patients in the Wegovy® 2.4 mg arm discontinued treatment compared with 3.5% in the placebo arm.[11]

Changes in waist circumference and select cardiometabolic parameters were evaluated as secondary endpoints (Table 4).[1]

STEP 3: Weight management in adults with intensive behavioral therapy

STEP 3 was a 68-week trial that enrolled 611 patients with obesity or with overweight and at least 1 weight-related comorbid condition; patients with type 2 diabetes were excluded.[1,7] The patients were randomized in a 2:1 ratio to receive either Wegovy® 2.4 mg (n=407) or placebo (n=204) (with a 16-week dose escalation period) in conjunction with intensive behavioral therapy. Patients were provided 30 individual intensive behavioral therapy visits with a registered dietician. Intensive behavioral therapy consisted of an initial 8-week low-calorie diet (1000-1200 kcal/day) followed by 60 weeks of a reduced calorie diet (1200-1800 kcal/day) and increased physical activity (100 min/week with gradual increase to 200 min/week).

For the coprimary end points (Figure 2), after 68 weeks, a statistically significant reduction in body weight was observed in patients treated with Wegovy® (-16.0%) compared with those treated with placebo (-5.7%). A greater proportion of patients achieved ≥5% weight reduction with Wegovy® (84.8%) compared with placebo (47.8%).[1] During the trial, 17% of patients in the Wegovy® arm discontinued treatment compared with 19% in the placebo arm.[7]

Changes in waist circumference and select cardiometabolic parameters were evaluated as secondary endpoints (Table 4).[1]

STEP 4: Sustained weight management in adults

STEP 4 was a 68-week trial that enrolled 902 patients with obesity or with overweight and at least 1 weight-related comorbid condition; patients with type 2 diabetes were excluded. After a 20-week run-in period, during which all patients received Wegovy® in addition to lifestyle modification, 803 patients were randomized in a 2:1 ratio to continue Wegovy® 2.4 mg (n=535) or placebo (n=268) for 48 weeks and both continued on lifestyle modification.[1]

For the primary end point (Figure 3), from randomization (week 20) to week 68, treatment with Wegovy® resulted in a statistically significant reduction in body weight (-7.9%) compared with placebo (+6.9%).[1]

Changes in waist circumference and select cardiometabolic parameters were evaluated as secondary endpoints (Table 4).[1]

Important Safety Information

Warnings and Precautions, continued

- **Hypoglycemia:** Wegovy® lowers blood glucose and can cause hypoglycemia. In a trial of adult patients with type 2 diabetes, hypoglycemia was reported in 6.2% of Wegovy® patients versus 2.5% of placebo patients. Patients with diabetes taking Wegovy® with an insulin or insulin secretagogue (e.g. sulfonylurea) may have an increased risk of hypoglycemia, including severe hypoglycemia. The use of Wegovy® in patients with type 1 diabetes or in combination with insulin has not been evaluated. Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms. Monitor blood glucose in patients with diabetes

FIGURE 2. Weight-Related Efficacy Endpoints[1,2]

	STEP 1 Baseline to Week 68		STEP 2 Baseline to Week 68		STEP 3 Baseline to Week 68		STEP 5 Baseline to Week 104		STEP TEENS Baseline to Week 68	
	Placebo n=655	Wegovy® n=1306	Placebo n=403	Wegovy® n=404	Placebo n=204	Wegovy® n=407	Placebo n=152	Wegovy® n=152	Placebo n=67	Wegovy® n=134
Baseline body weight (kg)	105.2	105.4	100.5	99.9	103.7	106.9	106.5	105.6	**Baseline BMI (kg/m²)** 35.7	37.7
Mean percent change in body weight	-2.4	-14.9	-3.4	-9.6	-5.7	-16.0	-2.6	-15.2	**Mean percent change in BMI** 0.6	-16.1
	Difference -12.4[a]		Difference -6.2[a]		Difference -10.3[a]		Difference -12.6[a]		Difference -16.7[a]	
Percent of patients with ≥5% reduction in body weight	31.1	83.5[a]	30.2	67.4[a]	47.8	84.8[a]	34.4[b]	77.1[a,b]	**Percent of patients with ≥5% reduction in BMI[c]** 19.7	77.1
Percent of patients with ≥10% reduction in body weight	12.0	66.1[a]	10.2	44.5[a]	27.1	73.0[a]	13.3[b]	61.8[a,b]	**Percent of patients with ≥10% reduction in BMI[c]** 7.7	65.1
Percent of patients with ≥15% reduction in body weight	4.8	47.9[a]	4.3	25.1[a]	13.2	53.4[a]	7.0[b]	52.1[a,b]	**Percent of patients with ≥15% reduction in BMI[c]** 4.0	57.8

Percent change in body weight: 0, -5, -10, -15, -20

Percent change in BMI: 5, 0, -5, -10, -15, -20

[a] $p<0.0001$ (unadjusted 2-sided) for superiority.

[b] Observed data include only patients who had a body weight assessment at week 104 (n=144 for Wegovy® arm and n=128 for placebo arm) and do not include all randomized patients.

[c] Parameters not included in the prespecified hierarchical testing.

STEP 5: Long-term weight management in adults

STEP 5 was a 104-week trial that enrolled 304 adult patients with obesity or with overweight and at least 1 weight-related comorbid condition; patients with diabetes were excluded.[2] Patients were randomized in a 1:1 ratio to either Wegovy® 2.4 mg (n=152) or placebo (n=152) (with a 16-week dose escalation period), both in conjunction with lifestyle modifications.[2]

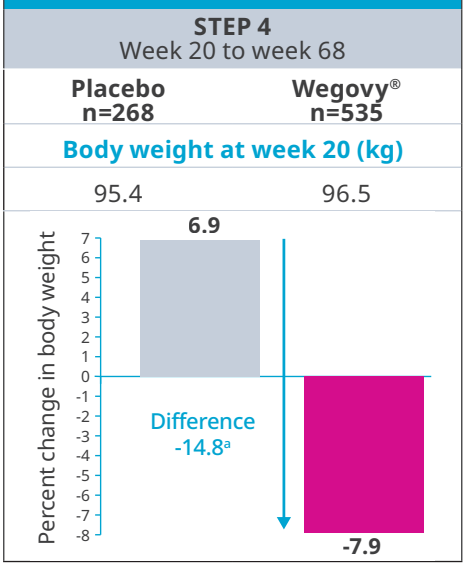
For the coprimary end points (Figure 2), after 104 weeks, a statistically significant reduction in body weight was observed in patients treated with Wegovy® (-15.2%) compared with those treated with placebo (-2.6%).[2] A greater proportion of patients achieved ≥5% weight reduction with Wegovy® (77.1%) compared with placebo (34.4%).[2] The proportions of patients who achieved ≥5% weight reduction are observed data, which include only patients who had a body weight assessment at week 104 (n=144 for Wegovy® arm and n=128 for placebo arm) and do not include all

Important Safety Information

Warnings and Precautions, continued

- **Acute Kidney Injury:** There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which in some cases required hemodialysis, in patients treated with semaglutide. Patients with renal impairment may be at a greater risk of acute kidney injury, but some events have been reported in patients without known underlying renal disease. A majority of the events occurred in patients who experienced nausea, vomiting, or diarrhea, leading to volume depletion. Monitor renal function when initiating or escalating doses of Wegovy® in patients reporting severe adverse gastrointestinal reactions and in patients with renal impairment reporting any adverse reactions that could lead to volume depletion

FIGURE 3. STEP 4 Primary Endpoint[1]



[a]*P*<0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity.

randomized patients. During the trial, 13% of patients in the Wegovy® arm discontinued treatment compared with 27% in the placebo arm.[2]

Changes in waist circumference and select cardiometabolic parameters were evaluated as secondary endpoints (Table 4).[2]

STEP TEENS: Pediatric study of patients aged ≥12 years

Wegovy® was evaluated in a 68-week trial in 201 pubertal pediatric patients aged 12 years and older with BMI corresponding to ≥95th percentile standardized for age and sex.[1] After a 12-week lifestyle run-in period (including dietary recommendations and physical activity counseling), patients were randomized 2:1 to Wegovy® once weekly (n=134) or placebo once weekly (n=67).[1] Wegovy® or matching placebo was escalated to 2.4 mg or maximally tolerated dose during

TABLE 3. STEP 6 Relevant Secondary Endpoint Results[1]

STEP 6 Baseline to week 68			
Intention-to-treat	Placebo n=101	Wegovy® 1.7 mg n=101	Wegovy® 2.4 mg n=199
Waist circumference (cm)[a]			
Change from baseline (LSMean[b])	-1.8	-7.7	-11.0
Difference from placebo (LSMean)		-5.9	-9.3
Systolic blood pressure (mmHg)[c]			
Change from baseline (LSMean[b])	-5.3	-10.8	-10.8
Difference from placebo (LSMean)		-5.4	-5.5
Diastolic blood pressure (mmHg)[c]			
Change from baseline (LSMean[b])	-2.2	-4.6	-5.3
Difference from placebo (LSMean)		-2.4	-3.1
Heart rate[c-e]			
Change from baseline (LSMean[b])	2.4	4.4	6.3
Difference from placebo (LSMean)		2.0	3.9
HbA1c (%)[c]			
Change from baseline (LSMean[b])	0.0	-0.9	-0.9
Difference from placebo (LSMean)		-0.9	-0.9
Total cholesterol (mg/dL)[c]			
Percent change from baseline (LSMean[b])	0.8	-6.6	-8.7
Relative difference from placebo (LSMean)		-7.3	-9.4
LDL cholesterol (mg/dL)[c]			
Percent change from baseline (LSMean[b])	-3.8	-10.1	-14.6
Relative difference from placebo (LSMean)		-6.5	-11.2
HDL cholesterol (mg/dL)[c]			
Percent change from baseline (LSMean[b])	5.9	6.7	9.2
Relative difference from placebo (LSMean)		0.7	3.1
Triglycerides (mg/dL)[c]			
Percent change from baseline (LSMean[b])	5.5	-19.5	-21.2
Relative difference from placebo (LSMean)		-23.7	-25.3

Missing data were imputed from retrieved subjects of the same randomized treatment arm (RD-MI). At baseline, 24.7% of patients had type 2 diabetes.

[a]Confirmatory secondary endpoint.

[b]Model-based estimates based on an analysis of a covariance model including treatment and type 2 diabetes status as factors and baseline values as a covariate.

[c]Supportive secondary endpoint. Supportive secondary endpoints were not included in the pre-specified hierarchical testing.

[d]Model-based estimates based on a mixed model for repeated measures including treatment and type 2 diabetes status as factors and baseline values as a covariate.

[e]Safety endpoint.

LSMean=least squares mean.

Important Safety Information

Warnings and Precautions, continued

- **Severe Gastrointestinal Adverse Reactions:** Use of Wegovy® has been associated with gastrointestinal adverse reactions, sometimes severe. In clinical trials, severe gastrointestinal adverse reactions were reported more frequently among patients receiving Wegovy® (4.1%) than placebo (0.9%). Wegovy® is not recommended in patients with severe gastroparesis

TABLE 4. STEP 1-5 and STEP TEENS Relevant Secondary Endpoint Results[1,2,12]

	STEP 1 Baseline to week 68		STEP 2 Baseline to week 68		STEP 3 Baseline to week 68		STEP 4 Week 20 to week 68		STEP 5 Baseline to week 104		STEP TEENS Baseline to week 68	
Intention-to-treat	Placebo n=655	Wegovy® n=1306	Placebo n=403	Wegovy® n=404	Placebo n=204	Wegovy® n=407	Placebo n=268	Wegovy® n=535	Placebo n=152	Wegovy® n=152	Placebo n=67	Wegovy® n=134
Waist circumference (cm)[a]											**Waist circumference (cm)[b,c]**	
Change from baseline (LSMean[c])	-4.1	-13.5	-4.5	-9.4	-6.3	-14.6	3.3	-6.4	-5.2	-14.4	-0.6	-12.7
Difference from placebo (LSMean)		-9.4		-4.9		-8.3		-9.7		-9.2		-12.1
Systolic blood pressure (mmHg)[a]											**Systolic blood pressure (mmHg)[b,c]**	
Change from baseline (LSMean[c])	-1.1	-6.2	-0.5	-3.9	-1.6	-5.6	4.4	0.5	-1.6	-5.7	-0.8	-2.7
Difference from placebo (LSMean)		-5.1		-3.4		-3.9		-3.9		-4.2		-1.9
Diastolic blood pressure (mmHg)[b]											**Diastolic blood pressure (mmHg)[b,c]**	
Change from baseline (LSMean[c])	-0.4	-2.8	-0.9	-1.6	-0.8	-3.0	0.9	0.3	-0.8	-4.4	-0.8	-1.4
Difference from placebo (LSMean)		-2.4		-0.7		-2.2		-0.5		-3.7		-0.6
Heart rate[d,e]											**Heart rate[d,e]**	
Change from baseline (LSMean)	-0.7	3.5	-0.2	2.5	2.1	3.1	-5.3	-2.0	-0.8	3.3	-2.3	1.2
Difference from placebo (LSMean)		4.3		2.7		1.0		3.3		4.1		3.5
HbA1c (%)[b]											**HbA1c (%)[b,c,f]**	
Change from baseline (LSMean[c])	-0.2	-0.4	-0.4	-1.6	-0.3	-0.5	0.1	-0.1	-0.1	-0.4	-0.1	-0.4
Difference from placebo (LSMean)		-0.3		-1.2		-0.2		-0.2		-0.3		-0.2
Total cholesterol (mg/dL)[b]											**Total cholesterol (mg/dL)[b,c]**	
Percent change from baseline (LSMean[c])	0.1	-3.3	-0.5	-1.4	2.1	-3.9	11.4	4.9	1.4	-3.3	-1.3	-8.3
Relative difference from placebo (LSMean)		-3.3		-0.9		-5.8		-5.8		-4.6		-7.1
LDL cholesterol (mg/dL)[b]											**LDL cholesterol (mg/dL)[b,c]**	
Percent change from baseline (LSMean[c])	1.3	-2.5	0.1	0.5	2.6	-4.7	7.6	1.1	-2.7	-6.1	-3.6	-9.9
Relative difference from placebo (LSMean)		-3.8		0.4		-7.1		-6.1		-3.4		-6.6
HDL cholesterol (mg/dL)[b]											**HDL cholesterol (mg/dL)[b,c]**	
Percent change from baseline (LSMean[c])	1.4	5.2	4.1	6.9	5.0	6.5	17.8	18.2	8.1	9.6	3.2	8.0
Relative difference from placebo (LSMean)		3.8		2.7		1.5		0.3		1.3		4.7
Triglycerides (mg/dL)[b]											**Triglycerides (mg/dL)[b,c]**	
Percent change from baseline (LSMean[c])	-7.3	-21.9	-9.4	-22.0	-6.5	-22.5	14.8	-5.6	3.7	-19.0	2.6	-28.4
Relative difference from placebo (LSMean)		-15.8		-13.9		-17.0		-17.8		-21.9		-30.2

Missing data for STEP 1-5 were imputed from retrieved subjects of the same randomized treatment arm (RD-MI). Missing data for STEP TEENS were imputed using available data according to value and timing of last available observation on treatment and end point's baseline value from retrieved subjects (RD-MI).

[a]Confirmatory secondary end point.

[b]Supportive secondary end point except for HbA1c in STEP 2, which was a confirmatory secondary endpoint. Supportive secondary end points were not included in the prespecified hierarchical testing.

[c]Model-based estimates based on an analysis of a covariance model including treatment (and stratification factors for STEP 2 and STEP TEENS only) as factors and baseline values as a covariate.

[d]Safety end point.

[e]Model-based estimates based on a mixed model for repeated measures including treatment (and stratification factors for STEP 2 only) as factors and baseline values as a covariate. In STEP TEENS, model-based estimates based on a mixed model for repeated measures including treatment as factors and baseline values as a covariate all nested within visit.

[f]In STEP TEENS, this was for patients without type 2 diabetes at randomization (n=129 for Wegovy®-treated patients and n=64 for placebo-treated patients).

Important Safety Information

Warnings and Precautions, continued

- **Hypersensitivity Reactions:** Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with Wegovy®. If hypersensitivity reactions occur, discontinue use of Wegovy®, treat promptly per standard of care, and monitor until signs and symptoms resolve. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist
- **Diabetic Retinopathy Complications in Patients with Type 2 Diabetes:** In a trial of adult patients with type 2 diabetes, diabetic retinopathy was reported by 4.0% of Wegovy® patients and 2.7% of placebo patients. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy

a 16-week period followed by 52 weeks on maintenance dose.[1] Of those patients who received Wegovy® and who completed the trial, 86.7% were on the 2.4 mg dose at the end of the trial; for 5% of patients, 1.7 mg was the maximum tolerated dose.[1] Both trial arms continued on diet and exercise/lifestyle modifications.

For the primary end point (Figure 2), after 68 weeks, treatment with Wegovy® resulted in a statistically significant reduction in percent BMI (-16.1%) compared with placebo (0.6%).[1] For the secondary supportive end point (Figure 2), greater proportions of patients treated with Wegovy® achieved a ≥5% reduction in baseline BMI (77.1%) than those treated with placebo (19.7%). Supportive secondary end points were not included in the statistical testing hierarchy and, as such, not controlled for multiplicity.[1,3] During the trial, 10% of patients in each of the Wegovy® and placebo arms discontinued treatment.[13]

Changes in waist circumference and select cardiometabolic parameters were evaluated as secondary endpoints (Table 4).[1]

STEP 6: Weight management in an East-Asian adult population

STEP 6 was a 68-week randomized trial that enrolled 401 East-Asian adult patients (Japan and South Korea) with BMI ≥35 kg/m^2 and at least 1 weight-related comorbid condition or with a BMI of 27 kg/m^2 to 34.9 kg/m^2 and at least 2 weight-related comorbid conditions. Patients were randomized in a 2:1:1 ratio to either Wegovy® 2.4 mg (n=199), Wegovy® 1.7 mg (n=101), or placebo (n=101), all in conjunction with lifestyle modifications.[1]

TABLE 5. STEP 1-3 Adverse Reactions (≥2% and Greater Than Placebo) in Wegovy®-Treated Adults With Obesity or Overweight for Chronic Weight Management[1]

	Placebo n=1261 %	Wegovy® 2.4 mg n=2116 %
Nausea	16	44
Diarrhea	16	30
Vomiting	6	24
Constipation	11	24
Abdominal pain[a]	10	20
Headache	10	14
Fatigue[b]	5	11
Dyspepsia	3	9
Dizziness	4	8
Abdominal distension	5	7
Eructation	<1	7
Hypoglycemia in T2D[c]	2	6
Flatulence	4	6
Gastroenteritis	4	6
Gastroesophageal reflux disease	3	5
Gastritis[d]	1	4
Gastroenteritis viral	3	4
Hair loss	1	3
Dysesthesia[e]	1	2

T2D=type 2 diabetes.

[a]Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, abdominal tenderness, abdominal discomfort, and epigastric discomfort.

[b]Includes fatigue and asthenia.

[c]Defined as blood glucose <54 mg/dL with or without symptoms of hypoglycemia or severe hypoglycemia (requiring the assistance of another person) in patients with type 2 diabetes not on concomitant insulin (STEP 2, Wegovy® n=403, Placebo n=402).

[d]Includes chronic gastritis, gastritis, gastritis erosive, and reflux gastritis.

[e]Includes paresthesia, hyperesthesia, burning sensation, allodynia, dysesthesia, skin burning sensation, pain of skin, and sensitive skin.

For the coprimary end points (Figure 4), after 68 weeks, a statistically significant reduction in body weight was observed in patients treated with Wegovy® 2.4 mg (-13.2%) and Wegovy® 1.7 mg (-9.6%) compared with those treated with placebo (-2.1%). A greater proportion of patients achieved ≥5% weight reduction with

Important Safety Information

Warnings and Precautions, continued

- **Heart Rate Increase:** Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed in Wegovy® adult patients compared to placebo in clinical trials. More Wegovy® adult patients compared with placebo had maximum changes from baseline of 10 to 19 bpm (41% versus 34%) and 20 bpm or more (26% versus 16%). In a clinical trial in pediatric patients aged 12 years and older with normal baseline heart rate, more patients treated with Wegovy® compared to placebo had maximum changes in heart rate of 20 bpm or more (54% versus 39%). Monitor heart rate at regular intervals and instruct patients to report palpitations or feelings of a racing heartbeat while at rest. If patients experience a sustained increase in resting heart rate, discontinue Wegovy®

FIGURE 4. STEP 6 Weight-Related Efficacy Endpoints[1]

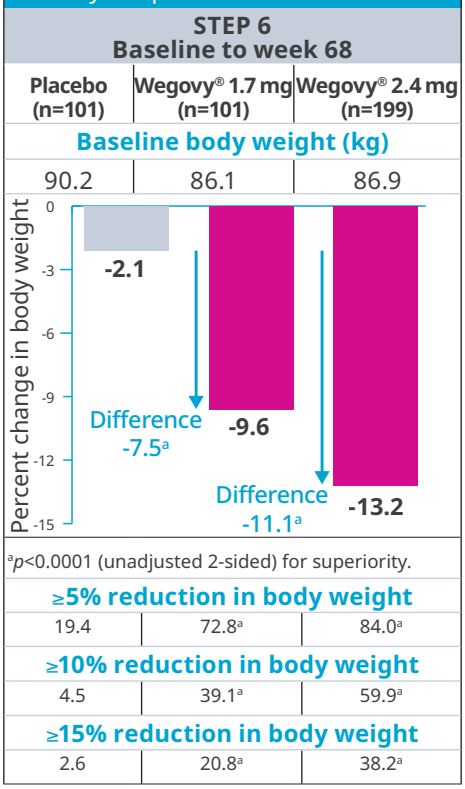


TABLE 6. STEP TEENS Adverse Reactions (≥3% and Greater Than Placebo) in Wegovy®-Treated Pediatric Patients Aged ≥12 Years With Obesity for Chronic Weight Management[1]

	Placebo n=67 %	Wegovy® 2.4 mg n=133 %
Nausea	18	42
Vomiting	10	36
Diarrhea	19	22
Headache	16	17
Abdominal pain	6	15
Nasopharyngitis	10	12
Dizziness	3	8
Gastroenteritis	3	7
Constipation	2	6
Gastroesophageal reflux disease	2	4
Sinusitis	2	4
Urinary tract infection	2	4
Ligament sprain	2	4
Anxiety	2	4
Hair Loss	0	4
Cholelithiasis	0	4
Eructation	0	4
Influenza	0	3
Rash	0	3
Urticaria	0	3

Wegovy® 2.4 mg (84.0%) and Wegovy® 1.7 mg (72.8%) compared with placebo (19.4%).[1] During the trial, 7%, 8%, and 3% of patients in the Wegovy® 2.4 mg, Wegovy® 1.7 mg, and placebo arms discontinued treatment, respectively.[14]

Changes in waist circumference and select cardiometabolic parameters were evaluated as secondary endpoints (Table 3).[1]

Adverse Reactions[1]

Adverse reactions reported in clinical trials are listed in Table 5 and Table 6. In STEP 1-3, common adverse reactions leading to discontinuation were nausea (1.8% versus 0.2%), vomiting (1.2% versus 0%), and diarrhea (0.7% versus 0%) for Wegovy® and placebo, respectively. Adverse reactions with Wegovy® treatment in pediatric patients aged 12 years and older were similar to those reported in adults. Pediatric patients aged 12 years and older treated with Wegovy® had greater incidences of cholelithiasis, cholecystitis, hypotension, rash, and urticaria compared to adults treated with Wegovy®.

In a cardiovascular outcomes trial, 8,803 patients were exposed to Wegovy® for a median of 37.3 months and 8,801

Important Safety Information

Warnings and Precautions, continued

- **Suicidal Behavior and Ideation:** Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients for depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue Wegovy® in patients who experience suicidal thoughts or behaviors and avoid in patients with a history of suicidal attempts or active suicidal ideation
- **Pulmonary Aspiration During General Anesthesia or Deep Sedation:** Wegovy® delays gastric emptying. There have been rare postmarketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking Wegovy®

patients were exposed to placebo for a median of 38.6 months. Safety data collection was limited to serious adverse events (including death), adverse events leading to discontinuation, and adverse events of special interest. Sixteen percent (16%) of Wegovy®-treated patients and 8% of placebo-treated patients, respectively, discontinued study drug due to an adverse event.

Dosage and Administration[1]

Wegovy® is available in 5 strengths: 0.25 mg/0.5 mL, 0.5 mg/0.5 mL, 1 mg/0.5 mL, 1.7 mg/0.75 mL, and 2.4 mg/0.75 mL. Wegovy® should be administered following the dose escalation schedule (Figure 5).

Dose escalation schedule[1]

- Initial dose of 0.25 mg injected subcutaneously once weekly followed by the dose escalation schedule to reduce the risk of gastrointestinal adverse reactions. If patients do not tolerate a dose during dose escalation, consider delaying dose escalation for 4 weeks
- The maintenance dosage of Wegovy® is either 2.4 mg (recommended) or 1.7 mg once-weekly. Consider treatment response and tolerability when selecting the maintenance dosage (Figure 5)
- In patients with type 2 diabetes, monitor blood glucose prior to starting Wegovy® and during Wegovy® treatment
- Not all patients will be escalated to the recommended dose by week 17—it is possible that some may require up to 32 weeks to reach this recommended dose

FIGURE 5. Wegovy® Dose Escalation Schedule[1]

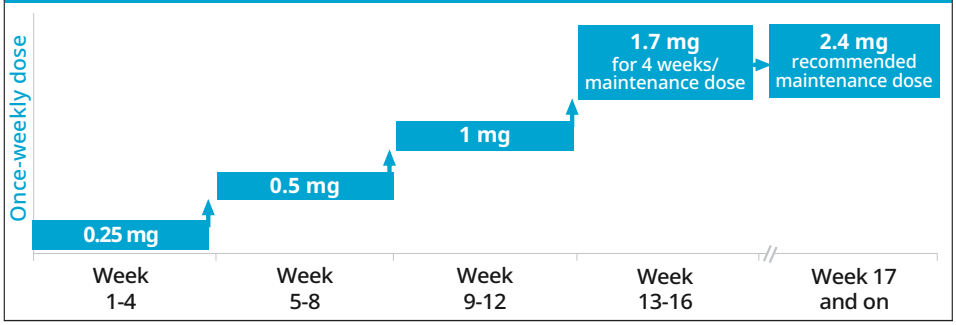


TABLE 7. Wegovy® Single-Dose Pen[1]

	Total Strength per Total Volume	NDC
	0.25 mg/0.5 mL	0169-4525-14
	0.5 mg/0.5 mL	0169-4505-14
	1 mg/0.5 mL	0169-4501-14
	1.7 mg/0.75 mL	0169-4517-14
	2.4 mg/0.75 mL	0169-4524-14

Wegovy® injection is supplied in a pre-filled, disposable, single-dose pen-injector with an integrated needle (Table 7). Store between 36°F and 46°F (2°C to 8°C). If needed, prior to cap removal, Wegovy® can be stored from 46°F to 86°F (8°C to 30°C) in the original carton for up to 28 days. Before using the Wegovy® pen for the first time, patients and caregivers should talk to healthcare providers about how to prepare and inject Wegovy® correctly. Wegovy® may be taken with or without food.

Summary[1]

Wegovy® is the only FDA approved GLP-1 RA that is proven to treat obesity and reduce the risk of MACE. It is indicated to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.

Important Safety Information

Adverse Reactions

Most common adverse reactions (incidence ≥5%) are: nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distention, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, gastroesophageal reflux disease, and nasopharyngitis

Drug Interactions

- The addition of Wegovy® in patients treated with insulin has not been evaluated. When initiating Wegovy®, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia
- Wegovy® causes a delay of gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. Monitor the effects of oral medications concomitantly administered with Wegovy®

Wegovy® is also indicated to reduce excess body weight and maintain weight reduction long term in:

- Adults and pediatric patients aged 12 years and older with obesity
- Adults with overweight in the presence of at least one weight-related comorbid condition

The SELECT trial assessed the safety and efficacy of Wegovy® in adults with established cardiovascular disease and overweight or obesity without diabetes. Wegovy® 2.4 mg significantly reduced the risk of first MACE occurrence (6.5%) compared to placebo (8%) when added to current standard of care, which included managing cardiovascular risk factors and individualized healthy lifestyle counseling (including diet and physical activity).

The safety and efficacy of Wegovy® were also evaluated in the STEP program, which included trials in adults and 1 in pediatric patients aged 12 and older.

In adults, treatment with Wegovy® resulted in a statistically significant percent reduction in body weight compared with placebo, both in combination with lifestyle modifications. Greater proportions of patients treated with Wegovy® achieved ≥5% weight reduction than those treated with placebo.

In STEP TEENS, treatment with Wegovy® resulted in a statistically significant percent reduction in BMI from baseline compared with placebo, both in combination with lifestyle modifications.

The most common adverse reactions were nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, gastroesophageal reflux disease, and nasopharyngitis.

Important Safety Information

Use in Specific Populations

- **Pregnancy:** May cause fetal harm. When pregnancy is recognized, discontinue Wegovy®. Discontinue Wegovy® in patients at least 2 months before a planned pregnancy
- **Pediatric:** Adverse reactions with Wegovy® in pediatric patients aged 12 years and older were similar to those reported in adults. Pediatric patients ≥12 years of age treated with Wegovy® had greater incidences of cholelithiasis, cholecystitis, hypotension, rash, and urticaria compared to adults treated with Wegovy®. There are insufficient data in pediatric patients with type 2 diabetes treated with Wegovy® for obesity to determine if there is an increased risk of hypoglycemia with Wegovy® treatment similar to that reported in adults
- **Geriatric:** In the cardiovascular outcomes trial, patients aged 75 years and older reported more hip and pelvis fractures on Wegovy® than placebo. Patients aged 75 years and older (Wegovy® and placebo) reported more serious adverse reactions overall compared to younger adult patients

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